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=> d his

     (FILE 'HOME' ENTERED AT 22:16:16 ON 10 MAR 2005)

     FILE 'REGISTRY' ENTERED AT 22:16:27 ON 10 MAR 2005
                E CYCLOPAMINE/CN
L1            1 S E3

     FILE 'MEDLINE, HCAPLUS, CANCERLIT' ENTERED AT 22:17:27 ON 10 MAR 2005
L2          134 S L1 AND (APOPTO? OR CANCER? OR TUMOUR? OR TUMOR? OR CARCINOM?
L3          106 DUP REM L2 (28 DUPLICATES REMOVED)
L4            8 S L3 AND (TOPICAL? OR OINTMENT? OR GEL? OR CREAM? OR SUSTAIN?(2

     FILE 'STNGUIDE' ENTERED AT 22:23:40 ON 10 MAR 2005

     FILE 'MEDLINE, HCAPLUS, CANCERLIT' ENTERED AT 22:27:23 ON 10 MAR 2005
L5           76 S L3 AND PY<=2003
L6           71 S L5 NOT L4

     FILE 'STNGUIDE' ENTERED AT 22:29:33 ON 10 MAR 2005

     FILE 'MEDLINE, HCAPLUS, CANCERLIT' ENTERED AT 22:33:48 ON 10 MAR 2005

=> s l5 and (therapeut? or antagon? or smooth? or steroid? or neurogen?)
L7          52 L5 AND (THERAPEUT? OR ANTAGON? OR SMOOTH? OR STEROID? OR NEUROG
               EN?)

=> d l7 abs cbib kwic 1-52

L7   ANSWER 1 OF 52     MEDLINE on STN
AB   Small-molecule antagonists of Hedgehog-pathway
     signaling, such as cyclopamine, have been known for some time.  Now,
     small-molecule agonists of the Hedgehog pathway have also been
     identified.  The finding that both antagonists and agonists
     target the protein Smoothened supports the emerging hypothesis
     that Smoothened may be regulated by endogenous small molecules.
2004353503.    PubMed ID: 12437769.    Roughing up Smoothened:
     chemical modulators of hedgehog signaling. King Randall W.
     (Institute of Chemistry and Cell Biology, Department of Cell Biology,
     Harvard Medical School, Boston, MA 02115, USA..
     randy_king@hms.harvard.edu) . Journal of biology (Online), (2002 Nov
     6) 1 (2) 8.  Electronic Publication: 2002-11-06. Ref: 17. Journal
     code: 101147570. ISSN: 1475-4924. Pub. country: England: United Kingdom.
     Language: English.
TI   Roughing up Smoothened: chemical modulators of hedgehog
     signaling.
SO   Journal of biology (Online), (2002 Nov 6) 1 (2) 8.  Electronic
     Publication: 2002-11-06. Ref: 17
     Journal code: 101147570. ISSN: 1475-4924.
AB   Small-molecule antagonists of Hedgehog-pathway
     signaling, such as cyclopamine, have been known for some time.  Now,
     small-molecule agonists of the Hedgehog pathway have also been
     identified.  The finding that both antagonists and agonists
     target the protein Smoothened supports the emerging hypothesis
     that Smoothened may be regulated by endogenous small molecules.
RN   4449-51-8 (cyclopamine)
```

CN 0 (Receptors, G-Protein-Coupled); 0 (SMO protein, human); 0 (Trans-Activators); 0 (Veratrum Alkaloids); 0 (**hedgehog** protein, vertebrate)

L7 ANSWER 2 OF 52 MEDLINE on STN

AB The involvement of **hedgehog** signaling in the initiation of osteoblastic **differentiation** in the bone collar during endochondral bone formation has been well established. The stages at which **hedgehog** acts during osteoblast **differentiation** as well as its molecular mechanism of action are less well understood. To address these questions, we have made use of the preosteoblastic cell line KS483. First, a systematic survey of mRNA expression of osteoblastic **differentiation** showed expression of Ihh and signaling intermediates at all stages. Interestingly, expression of Ihh, Gli1 and Ptc1 peaked during the maturation phase. Addition of recombinant human sonic **hedgehog** (rShh) potently increased osteoblastic **differentiation** of KS483 cells dose-dependently as assayed by a modest increase in alkaline phosphatase (ALP) activity, a strong increase in matrix mineralization, and increased mRNA expression of established osteoblast marker genes. These effects were blocked by the **hedgehog antagonist** cyclopamine, which by itself was ineffective. Addition of rShh during early stages was sufficient, while addition to mature osteoblasts had no effect. Furthermore, **hedgehog** signaling could be completely blocked by the BMP **antagonists,** soluble truncated BMPR-IA and noggin. In contrast, the BMP-induced **differentiation** of KS483 cells could only be partly inhibited by high doses of cyclopamine. These data demonstrate that Hh-induced osteoblastic **differentiation** requires functional BMP signaling. In KS483 cells, Hh and BMP synergistically induced alkaline phosphatase activity only when suboptimal concentrations of BMP were used. This synergy did not occur at the level of immediate early BMP response, but at the level of Hh response as determined by transient transfection studies using either a BMP reporter or a Gli reporter construct. In addition, rShh inhibited adipogenesis of KS483 cells cultured under adipogenic culture conditions, suggesting that Hh is involved in directing **differentiation** of KS483 cells toward osteoblasts at the expense of adipogenesis. Using in situ hybridization, we demonstrated, for the first time, Ihh mRNA expression in vivo in osteoblasts and lining cells in the humerus of developing human skeleton. Our in vitro and in vivo data indicate a stimulatory role for osteoblast-expressed Ihh in bone formation in a positive feedback loop. It may recruit progenitor cells in the osteoblastic lineage at the expense of adipocytes and it may stimulate maturation of early osteoblasts.

2003596800. PubMed ID: 14678849. **Hedgehog** stimulates only osteoblastic **differentiation** of undifferentiated KS483 cells. van der Horst Geertje; Farih-Sips Hetty; Lowik Clemens W G M; Karperien Marcel. (Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands. ) Bone, **(2003 Dec)** 33 (6) 899-910. Journal code: 8504048. ISSN: 8756-3282. Pub. country: United States. Language: English.

TI **Hedgehog** stimulates only osteoblastic **differentiation** of undifferentiated KS483 cells.

SO Bone, **(2003 Dec)** 33 (6) 899-910.
Journal code: 8504048. ISSN: 8756-3282.

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which **hedgehog** acts during osteoblast **differentiation** as well as its molecular mechanism of action are less well understood. To address these questions, we have made use of the preosteoblastic cell line KS483. First, a systematic survey of mRNA expression of osteoblastic **differentiation** showed expression of Ihh and signaling intermediates at all stages. Interestingly, expression of Ihh, Gli1 and Ptc1 peaked during the maturation phase. Addition of recombinant human sonic **hedgehog** (rShh) potently increased osteoblastic **differentiation** of KS483 cells dose-dependently as assayed by a modest increase in alkaline phosphatase (ALP) activity, a strong increase in matrix mineralization, and increased mRNA expression of established osteoblast marker genes. These effects were blocked by the **hedgehog antagonist** cyclopamine, which by itself was ineffective. Addition of rShh during early stages was sufficient, while addition to mature osteoblasts had no effect. Furthermore, **hedgehog** signaling could be completely blocked by the BMP **antagonists,** soluble truncated BMPR-IA and noggin. In contrast, the BMP-induced **differentiation** of KS483 cells could only be partly inhibited by high doses of cyclopamine. These data demonstrate that Hh-induced osteoblastic **differentiation** requires functional BMP signaling. In KS483 cells, Hh and BMP synergistically induced alkaline phosphatase activity only when suboptimal concentrations of. . . . In addition, rShh inhibited adipogenesis of KS483 cells cultured under adipogenic culture conditions, suggesting that Hh is involved in directing **differentiation** of KS483 cells toward osteoblasts at the expense of adipogenesis. Using in situ hybridization, we demonstrated, for the first time,. . . .

CT Adipocytes: CY, cytology
Adipocytes: PH, physiology
Alkaline Phosphatase: GE, genetics
Alkaline Phosphatase: ME, metabolism
Animals
Bone Development: PH, physiology
**Bone Morphogenetic Proteins: AI, antagonists & inhibitors**
Bone Morphogenetic Proteins: GE, genetics
Bone Morphogenetic Proteins: ME, metabolism
Bone Morphogenetic Proteins: PD, pharmacology
Calcification, Physiologic: DE, drug effects
Calcification, Physiologic: PH, physiology
**Cell Differentiation: DE, drug effects**
**Cell Differentiation: GE, genetics**
***Cell Differentiation: PH, physiology**
Cell Line
DNA-Binding Proteins: GE, genetics
Gene Expression Regulation: DE, drug effects
Genes, Reporter: GE, genetics
Humans
. . . . Humerus: EM, embryology
In Situ Hybridization
Indomethacin: PD, pharmacology
Infant
Kinetics
Membrane Proteins: GE, genetics
Membrane Proteins: ME, metabolism
Mice
**Neoplasm Proteins: GE, genetics**
**Neoplasm Proteins: ME, metabolism**

Oncogene Proteins: GE, genetics
Oncogene Proteins: ME, metabolism
Osteoblasts: DE, drug effects
Osteoblasts: ME, metabolism
*Osteoblasts:. . .

RN 104982-03-8 (Osteocalcin); **4449-51-8 (cyclopamine)**; 53-86-1 (Indomethacin)

CN 0 (Bone Morphogenetic Proteins); 0 (DNA-Binding Proteins); 0 (Gli protein); 0 (MSX2 protein); 0 (Membrane Proteins); 0 (**Neoplasm** Proteins); 0 (Oncogene Proteins); 0 (Receptors, G-Protein-Coupled); 0 (Recombinant Proteins); 0 (Runx2 protein); 0 (SMO protein, human); 0 (Smo protein,. . . mouse); 0 (Trans-Activators); 0 (Transcription Factors); 0 (Veratrum Alkaloids); 0 (bone morphogenetic protein 4); 0 (bone morphogenetic protein 6); 0 (**hedgehog** protein, vertebrate); 0 (osterix protein, mouse); 0 (patched protein, vertebrate); EC 3.1.3.1 (Alkaline Phosphatase)

L7 ANSWER 3 OF 52 MEDLINE on STN

AB Basal cell **carcinomas** and squamous cell **carcinomas** are the most common human **cancers** and increasing in incidence. The development of novel, pathogenesis-based therapies requires a better knowledge of the molecular mechanisms leading to the development of these **tumors**. Basal cell **carcinomas** are characterized by aberrant activation of Sonic-**Hedgehog** (SHH) signaling due to mutations in the PTCH or SMOH genes. In addition, about 50% of the cases carry mutations in the TP53 **tumor** suppressor gene. Squamous cell **carcinomas** lack alterations of SHH signaling, while TP53 mutations are detectable in virtually all cases. Alterations in cell cycle regulatory genes, such as CDKN2A, are also common. Recently, specific inhibitors of the SHH-signaling pathway have been developed and shown promising results in preclinical studies on experimental basal cell **carcinomas**. However, the clinical significance of such targeted molecular therapy remains to be evaluated. Another successful pathogenesis-based therapy, which is already in clinical use, is the administration of topic immune response modifier imiquimod. This drug can eradicate non-melanoma skin **cancers** by different mechanisms, including cytokine-mediated stimulation of the anti-**tumor** immune response, as well as the induction of **tumor** cell **apoptosis**.

2003554026. PubMed ID: 14634745. [Cutaneous epithelial **tumors**. Molecular biology and pathogenesis-based therapy]. Molekulare Grundlagen und pathogeneseorientierte Therapie epithelialer **Tumoren** der Haut. Reifenberger J; Schon M P. (Universitats-Hautklinik, Heinrich-Heine-Universitat, Dusseldorf.. Reifenbergerj@med.uni-duesseldorf.de) . Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete, **(2003 Dec)** 54 (12) 1164-70. Journal code: 0372755. ISSN: 0017-8470. Pub. country: Germany: Germany, Federal Republic of. Language: German.

TI [Cutaneous epithelial **tumors**. Molecular biology and pathogenesis-based therapy].
Molekulare Grundlagen und pathogeneseorientierte Therapie epithelialer **Tumoren** der Haut.

SO Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete, **(2003 Dec)** 54 (12) 1164-70.
Journal code: 0372755. ISSN: 0017-8470.

AB Basal cell **carcinomas** and squamous cell **carcinomas** are the most common human **cancers** and increasing in incidence. The

development of novel, pathogenesis-based therapies requires a better knowledge of the molecular mechanisms leading to the development of these **tumors**. Basal cell **carcinomas** are characterized by aberrant activation of Sonic-**Hedgehog** (SHH) signaling due to mutations in the PTCH or SMOH genes. In addition, about 50% of the cases carry mutations in the TP53 **tumor** suppressor gene. Squamous cell **carcinomas** lack alterations of SHH signaling, while TP53 mutations are detectable in virtually all cases. Alterations in cell cycle regulatory genes,. . . specific inhibitors of the SHH-signaling pathway have been developed and shown promising results in preclinical studies on experimental basal cell **carcinomas**. However, the clinical significance of such targeted molecular therapy remains to be evaluated. Another successful pathogenesis-based therapy, which is already in clinical use, is the administration of topic immune response modifier imiquimod. This drug can eradicate non-melanoma skin **cancers** by different mechanisms, including cytokine-mediated stimulation of the anti-**tumor** immune response, as well as the induction of **tumor** cell **apoptosis**.

CT Check Tags: Comparative Study
**Adjuvants, Immunologic: TU, therapeutic use**
Alleles
**Aminoquinolines: TU, therapeutic use**
Animals
**Antineoplastic Agents: TU, therapeutic use**
**Apoptosis**
**Carcinoma, Basal Cell: DT, drug therapy**
**Carcinoma, Basal Cell: ET, etiology**
***Carcinoma, Basal Cell: GE, genetics**
**Carcinoma, Basal Cell: IM, immunology**
***Carcinoma, Basal Cell: TH, therapy**
**Carcinoma, Squamous Cell: DT, drug therapy**
**Carcinoma, Squamous Cell: ET, etiology**
***Carcinoma, Squamous Cell: GE, genetics**
**Carcinoma, Squamous Cell: IM, immunology**
***Carcinoma, Squamous Cell: TH, therapy**
**Cerebellar Neoplasms: DT, drug therapy**
Disease Models, Animal
English Abstract
**Genes, Tumor Suppressor**
Humans
Medulloblastoma: DT, drug therapy
Membrane Proteins: GE, genetics
Mice
*Mutation
Signal Transduction: GE, genetics
**Skin Neoplasms: DT, drug therapy**
**Skin Neoplasms: ET, etiology**
***Skin Neoplasms: GE, genetics**
**Skin Neoplasms: IM, immunology**
***Skin Neoplasms: TH, therapy**
Trans-Activators
Transcription Factors: GE, genetics
**Tumor Cells, Cultured**
**Veratrum Alkaloids: TU, therapeutic use**

RN **4449-51-8 (cyclopamine)**; 99011-02-6 (imiquimod)

CN. . . 0 (Membrane Proteins); 0 (PTCH2 protein, human); 0 (Ptch2 protein, mouse); 0 (Trans-Activators); 0 (Transcription Factors); 0 (Veratrum

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    Alkaloids); 0 (hedgehog protein, vertebrate)

L7  ANSWER 4 OF 52    MEDLINE on STN
AB  Cortical progenitors are competent to produce interneurons, but do not
    generate large numbers of interneurons in vivo under normal circumstances.
    This could reflect the absence of an inductive signal in the environment
    of the dorsal telencephalon and/or the presence of an inhibitory signal.
    To determine whether either or both mechanisms regulate interneuron
    generation, progenitors in dorsomedial and dorsolateral wall explants of
    mouse telencephalon were marked with a retrovirus and cultured under
    several conditions.  When cultured separately, progenitors in dorsomedial
    wall explants produced fewer GABAergic interneurons than progenitors in
    dorsolateral wall explants.  When cocultured with ventral telencephalic
    cells, however, dorsomedial wall progenitors produced more GABAergic
    interneurons than in dorsomedial wall explants alone.  The inductive
    effect of ventral telencephalon depended on sonic hedgehog (Shh)
    and could be mimicked by exogenous Shh.  In contrast, exogenous bone
    morphogenetic protein 4 (BMP4) reduced the production of interneurons in
    dorsolateral wall explants and inhibited the induction by exogenous Shh.
    Moreover, inhibiting BMP signaling in dorsomedial wall progenitors with a
    dominant-negative BMP receptor Ib (dnBMPIb) virus increased their
    production of interneurons, even if Shh was blocked.  Shh and dnBMPRIb
    increased proliferation and the generation of interneurons, but FGF2 did
    not induce interneurons, although it increased proliferation.  This
    suggests that proliferation per se does not control the production of
    interneurons.  Our findings suggest that the generation of interneurons by
    dorsal telencephalic progenitors is normally limited by excess levels of
    BMPs.  Shh may promote the generation of interneurons by
    antagonizing BMP, but may not be required directly for the
    generation of interneurons.
2003509664.    PubMed ID: 14586015.   Sonic hedgehog and bone
    morphogenetic protein regulate interneuron development from dorsal
    telencephalic progenitors in vitro. Gulacsi Alexandra; Lillien Laura.
    (Department of Neurobiology and Pittsburgh Cancer Institute, University of
    Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA. )
    Journal of neuroscience : official journal of the Society for
    Neuroscience, (2003 Oct 29) 23 (30) 9862-72.  Journal code:
    8102140. ISSN: 1529-2401. Pub. country: United States. Language: English.
TI  Sonic hedgehog and bone morphogenetic protein regulate
    interneuron development from dorsal telencephalic progenitors in vitro.
SO  Journal of neuroscience : official journal of the Society for
    Neuroscience, (2003 Oct 29) 23 (30) 9862-72.
    Journal code: 8102140. ISSN: 1529-2401.
AB   . . .  progenitors produced more GABAergic interneurons than in
    dorsomedial wall explants alone.  The inductive effect of ventral
    telencephalon depended on sonic hedgehog (Shh) and could be
    mimicked by exogenous Shh.  In contrast, exogenous bone morphogenetic
    protein 4 (BMP4) reduced the production of.  .  .  by dorsal telencephalic
    progenitors is normally limited by excess levels of BMPs.  Shh may promote
    the generation of interneurons by antagonizing BMP, but may not
    be required directly for the generation of interneurons.
CT   Animals
       Antigens, Differentiation: BI, biosynthesis
     Bone Morphogenetic Proteins: PD, pharmacology
    *Bone Morphogenetic Proteins: PH, physiology
       Cell Differentiation: DE, drug effects
       Cell Differentiation: PH, physiology
```

Cell Division: PH, physiology
Cell Lineage
Cells, Cultured
Gene Transfer Techniques
Genes, Dominant
Genes, Reporter
Glutamic. . . physiology
*Stem Cells: CY, cytology
Stem Cells: DE, drug effects
*Stem Cells: ME, metabolism
*Telencephalon: CY, cytology
Telencephalon: EM, embryology
**Trans-Activators: AI, antagonists & inhibitors**
Trans-Activators: PD, pharmacology
*Trans-Activators: PH, physiology
Veratrum Alkaloids: PD, pharmacology
gamma-Aminobutyric Acid: ME, metabolism

RN **4449-51-8 (cyclopamine)**; 56-12-2 (gamma-Aminobutyric Acid); 56-86-0 (Glutamic Acid)

CN 0 (Antigens, **Differentiation**); 0 (Bone Morphogenetic Proteins); 0 (Receptors, Growth Factor); 0 (Trans-Activators); 0 (Veratrum Alkaloids); 0 (bone morphogenetic protein 4); 0 (**hedgehog** protein, vertebrate); EC 2.7.1.- (bone morphogenetic protein receptor type I); EC 2.7.1.37 (Protein-Serine-Threonine Kinases)

L7 ANSWER 5 OF 52 MEDLINE on STN

AB Activation of the **Hedgehog** (Hh) signalling pathway by sporadic mutations or in familial conditions such as Gorlin's syndrome is associated with **tumorigenesis** in skin, the cerebellum and skeletal muscle. Here we show that a wide range of digestive tract **tumours**, including most of those originating in the oesophagus, stomach, biliary tract and pancreas, but not in the colon, display increased Hh pathway activity, which is suppressible by cyclopamine, a Hh pathway **antagonist**. Cyclopamine also suppresses cell growth in vitro and causes durable regression of xenograft **tumours** in vivo. Unlike in Gorlin's syndrome **tumours**, pathway activity and cell growth in these digestive tract **tumours** are driven by endogenous expression of Hh ligands, as indicated by the presence of Sonic **hedgehog** and Indian **hedgehog** transcripts, by the pathway- and growth-inhibitory activity of a Hh-neutralizing antibody, and by the dramatic growth-stimulatory activity of exogenously added Hh ligand. Our results identify a group of common lethal malignancies in which Hh pathway activity, essential for **tumour** growth, is activated not by mutation but by ligand expression.

2003497716. PubMed ID: 14520411. Widespread requirement for **Hedgehog** ligand stimulation in growth of digestive tract **tumours**. Berman David M; Karhadkar Sunil S; Maitra Anirban; Montes De Oca Rocio; Gerstenblith Meg R; Briggs Kimberly; Parker Antony R; Shimada Yutaka; Eshleman James R; Watkins D Neil; Beachy Philip A. (Department of Molecular Biology and Genetics and Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. ) Nature, **(2003 Oct 23)** 425 (6960) 846-51. Electronic Publication: 2003-09-14. Journal code: 0410462. ISSN: 1476-4687. Pub. country: England: United Kingdom. Language: English.

TI Widespread requirement for **Hedgehog** ligand stimulation in growth of digestive tract **tumours**.

SO Nature, **(2003 Oct 23)** 425 (6960) 846-51. Electronic

Publication: 2003-09-14.
Journal code: 0410462. ISSN: 1476-4687.

AB Activation of the **Hedgehog** (Hh) signalling pathway by sporadic mutations or in familial conditions such as Gorlin's syndrome is associated with **tumorigenesis** in skin, the cerebellum and skeletal muscle. Here we show that a wide range of digestive tract **tumours,** including most of those originating in the oesophagus, stomach, biliary tract and pancreas, but not in the colon, display increased Hh pathway activity, which is suppressible by cyclopamine, a Hh pathway **antagonist**. Cyclopamine also suppresses cell growth in vitro and causes durable regression of xenograft **tumours** in vivo. Unlike in Gorlin's syndrome **tumours,** pathway activity and cell growth in these digestive tract **tumours** are driven by endogenous expression of Hh ligands, as indicated by the presence of Sonic **hedgehog** and Indian **hedgehog** transcripts, by the pathway- and growth-inhibitory activity of a Hh-neutralizing antibody, and by the dramatic growth-stimulatory activity of exogenously added Hh ligand. Our results identify a group of common lethal malignancies in which Hh pathway activity, essential for **tumour** growth, is activated not by mutation but by ligand expression.

CT Animals
Cell Division: DE, drug effects
**Cell Line, Tumor**
Digestive System: CY, cytology
Digestive System: DE, drug effects
Digestive System: ME, metabolism
Digestive System: PA, pathology
**Gastrointestinal Neoplasms: DT, drug therapy**
**Gastrointestinal Neoplasms: GE, genetics**
***Gastrointestinal Neoplasms: ME, metabolism**
***Gastrointestinal Neoplasms: PA, pathology**
Gene Deletion
***Gene Expression Regulation, Neoplastic**
Humans
Ligands
Membrane Proteins: GE, genetics
Membrane Proteins: ME, metabolism
Mice
Mice, Nude
Mutation
**Neoplasm Transplantation**
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
**RNA, Neoplasm: GE, genetics**
**RNA, Neoplasm: ME, metabolism**
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
*Signal Transduction
Signal Transduction: DE, drug effects
**Trans-Activators: AI, antagonists & inhibitors**
*Trans-Activators: GE, genetics
*Trans-Activators: ME, metabolism
Transplantation, Heterologous
Veratrum Alkaloids: PD, pharmacology
**Veratrum Alkaloids: TU, therapeutic use**

RN **4449-51-8 (cyclopamine)**

CN 0 (Ligands); 0 (Membrane Proteins); 0 (RNA, Messenger); 0 (RNA,

**Neoplasm**); 0 (Trans-Activators); 0 (Veratrum Alkaloids); 0 (**hedgehog** protein, vertebrate); 0 (patched protein, vertebrate)

L7 ANSWER 6 OF 52 MEDLINE on STN

2003497007. PubMed ID: 14574396. **Cancer**: a twist in a **hedgehog**'s tale. Scott Matthew P. Nature, **(2003 Oct 23)** 425 (6960) 780-2. Journal code: 0410462. ISSN: 1476-4687. Pub. country: England: United Kingdom. Language: English.

TI **Cancer**: a twist in a **hedgehog**'s tale.

SO Nature, **(2003 Oct 23)** 425 (6960) 780-2.
Journal code: 0410462. ISSN: 1476-4687.

CT Animals
Cell Division: DE, drug effects
**Gastrointestinal Neoplasms: DT, drug therapy**
***Gastrointestinal Neoplasms: GE, genetics**
***Gastrointestinal Neoplasms: ME, metabolism**
**Gastrointestinal Neoplasms: PA, pathology**
***Gene Expression Regulation, Neoplastic**
Humans
Membrane Proteins: GE, genetics
Membrane Proteins: ME, metabolism
**Receptors, G-Protein-Coupled: AI, antagonists & inhibitors**
Receptors, G-Protein-Coupled: GE, genetics
Receptors, G-Protein-Coupled: ME, metabolism
*Signal Transduction
Signal Transduction: DE, drug effects
**Trans-Activators: AI, antagonists & inhibitors**
*Trans-Activators: GE, genetics
*Trans-Activators: ME, metabolism
Veratrum Alkaloids: PD, pharmacology
**Veratrum Alkaloids: TU, therapeutic use**

RN **4449-51-8 (cyclopamine)**

CN 0 (Membrane Proteins); 0 (Receptors, G-Protein-Coupled); 0 (SMO protein, human); 0 (Trans-Activators); 0 (Veratrum Alkaloids); 0 (**hedgehog** protein, vertebrate); 0 (patched protein, vertebrate)

L7 ANSWER 7 OF 52 MEDLINE on STN

AB **Hedgehog** signalling--an essential pathway during embryonic pancreatic development, the misregulation of which has been implicated in several forms of **cancer**--may also be an important mediator in human pancreatic **carcinoma**. Here we report that sonic **hedgehog**, a secreted **hedgehog** ligand, is abnormally expressed in pancreatic **adenocarcinoma** and its precursor lesions: pancreatic intraepithelial **neoplasia** (PanIN). Pancreata of Pdx-Shh mice (in which Shh is misexpressed in the pancreatic endoderm) develop abnormal tubular structures, a phenocopy of human PanIN-1 and -2. Moreover, these PanIN-like lesions also contain mutations in K-ras and overexpress HER-2/neu, which are genetic mutations found early in the progression of human pancreatic **cancer**. Furthermore, **hedgehog** signalling remains active in cell lines established from primary and metastatic pancreatic **adenocarcinomas**. Notably, inhibition of **hedgehog** signalling by cyclopamine induced **apoptosis** and blocked proliferation in a subset of the pancreatic **cancer** cell lines both in vitro and in vivo. These data suggest that this pathway may have an early and critical role in the genesis of this **cancer**, and that maintenance of **hedgehog** signalling is important for aberrant proliferation and

**tumorigenesis**.
2003496981. PubMed ID: 14520413. **Hedgehog** is an early and late mediator of pancreatic **cancer tumorigenesis**. Thayer Sarah P; di Magliano Marina Pasca; Heiser Patrick W; Nielsen Corinne M; Roberts Drucilla J; Lauwers Gregory Y; Qi Yan Ping; Gysin Stephan; Fernandez-del Castillo Carlos; Yajnik Vijay; Antoniu Bozena; McMahon Martin; Warshaw Andrew L; Hebrok Matthias. (Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.. sthayer@partners.org) . Nature, **(2003 Oct 23)** 425 (6960) 851-6. Electronic Publication: 2003-09-14. Journal code: 0410462. ISSN: 1476-4687. Pub. country: England: United Kingdom. Language: English.

TI **Hedgehog** is an early and late mediator of pancreatic **cancer tumorigenesis**.

SO Nature, **(2003 Oct 23)** 425 (6960) 851-6. Electronic Publication: 2003-09-14.
Journal code: 0410462. ISSN: 1476-4687.

AB **Hedgehog** signalling--an essential pathway during embryonic pancreatic development, the misregulation of which has been implicated in several forms of **cancer**--may also be an important mediator in human pancreatic **carcinoma**. Here we report that sonic **hedgehog**, a secreted **hedgehog** ligand, is abnormally expressed in pancreatic **adenocarcinoma** and its precursor lesions: pancreatic intraepithelial **neoplasia** (PanIN). Pancreata of Pdx-Shh mice (in which Shh is misexpressed in the pancreatic endoderm) develop abnormal tubular structures, a phenocopy. . . also contain mutations in K-ras and overexpress HER-2/neu, which are genetic mutations found early in the progression of human pancreatic **cancer**. Furthermore, **hedgehog** signalling remains active in cell lines established from primary and metastatic pancreatic **adenocarcinomas**. Notably, inhibition of **hedgehog** signalling by cyclopamine induced **apoptosis** and blocked proliferation in a subset of the pancreatic **cancer** cell lines both in vitro and in vivo. These data suggest that this pathway may have an early and critical role in the genesis of this **cancer**, and that maintenance of **hedgehog** signalling is important for aberrant proliferation and **tumorigenesis**.

CT **Adenocarcinoma: DT, drug therapy**
  **Adenocarcinoma: GE, genetics**
  **Adenocarcinoma: ME, metabolism**
  **Adenocarcinoma: PA, pathology**
 Animals
  **Apoptosis: DE, drug effects**
 Cell Division: DE, drug effects
  **Cell Line, Tumor**
  ***Cell Transformation, Neoplastic**
  ***Gene Expression Regulation, Neoplastic**
 Genes, erbB-2: GE, genetics
 Genes, ras: GE, genetics
 Humans
 Mice
 Mice, Nude
 Mutation
  **Neoplasm Transplantation**
  **Pancreatic Neoplasms: DT, drug therapy**
  **Pancreatic Neoplasms: GE, genetics**
  ***Pancreatic Neoplasms: ME, metabolism**

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FILE 'MEDLINE' ENTERED AT 22:17:27 ON 10 MAR 2005

FILE 'HCAPLUS' ENTERED AT 22:17:27 ON 10 MAR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'CANCERLIT' ENTERED AT 22:17:27 ON 10 MAR 2005

=> d his

     (FILE 'HOME' ENTERED AT 22:16:16 ON 10 MAR 2005)

     FILE 'REGISTRY' ENTERED AT 22:16:27 ON 10 MAR 2005
                E CYCLOPAMINE/CN
L1            1 S E3

     FILE 'MEDLINE, HCAPLUS, CANCERLIT' ENTERED AT 22:17:27 ON 10 MAR 2005

=> s l1 and (apopto? or cancer? or tumour? or tumor? or carcinom? or adenom? or
adenocarcinom? or neoplas? or leukem? or lymphom? or hedgehog? or differentiat?)
L2          134 L1 AND (APOPTO? OR CANCER? OR TUMOUR? OR TUMOR? OR CARCINOM? OR
               ADENOM? OR ADENOCARCINOM? OR NEOPLAS? OR LEUKEM? OR LYMPHOM? OR
               HEDGEHOG? OR DIFFERENTIAT?)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3          106 DUP REM L2 (28 DUPLICATES REMOVED)

=> s l3 and (topical? or ointment? or gel? or cream? or sustain?(2a)releas? or
cosmetic?)
L4            8 L3 AND (TOPICAL? OR OINTMENT? OR GEL? OR CREAM? OR SUSTAIN?(2A)
               RELEAS? OR COSMETIC?)

=> d l4 abs cbib kwic 1-8

L4   ANSWER 1 OF 8     MEDLINE on STN
2004468016.    PubMed ID: 15316158.   Cyclopamine, hedgehog and
     psoriasis. Kuenzli Stephane; Sorg Olivier; Saurat Jean-Hilaire.
     Dermatology (Basel, Switzerland), (2004) 209 (2) 81-3.  Journal code:
     9203244. ISSN: 1018-8665. Pub. country: Switzerland. Language: English.
TI   Cyclopamine, hedgehog and psoriasis.
CT   Check Tags: Comparative Study
        Administration, Topical
      Humans
      Prospective Studies
     *Psoriasis: DT, drug therapy
     *Psoriasis: PA, pathology
      Sensitivity and Specificity
      Treatment Outcome
     *Veratrum Alkaloids: TU,.  .  .
RN   4449-51-8 (cyclopamine)

L4   ANSWER 2 OF 8     MEDLINE on STN
AB   BACKGROUND: We have earlier found a highly efficient induction of the
     differentiation of epidermal lineage skin tumors by
     cyclopamine, a steroidal alkaloid inhibitor of the hedgehog
     /smoothened signaling, under conditions in which cyclopamine exerted no
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adverse effect on skin. OBJECTIVE: We aimed to develop a mechanism-based treatment for psoriasis with cyclopamine. METHODS: We subjected psoriatic skin lesions to cyclopamine under conditions similar to those we used for skin **tumors** and evaluated the responses of lesions clinically and by histopathological/immunohistochemical analyses. RESULTS: All treated lesions in different patients having plaque and guttate forms of psoriasis regressed rapidly. **Differentiation** of the epidermal cells of lesional skin and disappearances of infiltrating inflammatory cells were evident within a day. Lesions were cleared commonly on days 3-4. Former treatment sites followed up for more than 24 months now show a lack of adverse effects in the long term. CONCLUSION: An effective treatment for psoriasis is described, consistent with intervention in a proximal/key pathogenic event.

2004411249. PubMed ID: 15316166. Rapid clearance of psoriatic skin lesions induced by **topical** cyclopamine. A preliminary proof of concept study. Tas Sinan; Avci Oktay. (Yasemin Sokak Number 6, Narlidere, Manavkuyu Mahallesi 244 Sokak, 5-1/2 Bornova, Izmir, Turkey. ) Dermatology (Basel, Switzerland), (2004) 209 (2) 126-31. Journal code: 9203244. ISSN: 1018-8665. Pub. country: Switzerland. Language: English.

TI Rapid clearance of psoriatic skin lesions induced by **topical** cyclopamine. A preliminary proof of concept study.

AB BACKGROUND: We have earlier found a highly efficient induction of the **differentiation** of epidermal lineage skin **tumors** by cyclopamine, a steroidal alkaloid inhibitor of the **hedgehog** /smoothened signaling, under conditions in which cyclopamine exerted no adverse effect on skin. OBJECTIVE: We aimed to develop a mechanism-based treatment. . . psoriasis with cyclopamine. METHODS: We subjected psoriatic skin lesions to cyclopamine under conditions similar to those we used for skin **tumors** and evaluated the responses of lesions clinically and by histopathological/immunohistochemical analyses. RESULTS: All treated lesions in different patients having plaque and guttate forms of psoriasis regressed rapidly. **Differentiation** of the epidermal cells of lesional skin and disappearances of infiltrating inflammatory cells were evident within a day. Lesions were. . .

CT Check Tags: Comparative Study; Female; Male
**Administration, Topical**
Adult
Biopsy, Needle
Dose-Response Relationship, Drug
Drug Administration Schedule
Follow-Up Studies
Humans
Immunohistochemistry
Middle Aged
Prospective Studies
*Psoriasis:. . .

RN **4449-51-8 (cyclopamine)**

L4 ANSWER 3 OF 8 MEDLINE on STN

AB **Hedgehog**/smoothened signaling is active in a variety of **tumors** and is also involved in the maintenance of normal stem cells in vivo. We evaluated the possibility of preferential affection of **tumor** versus normal cells following inhibition of this signaling. We applied a **cream** preparation of cyclopamine (an inhibitor of the **hedgehog**/smoothened signaling) onto skin **tumors** in patients who were scheduled for the excision of these **tumors** (four basal cell **carcinomas** and a trichoepithelioma in four unrelated patients). All of the cyclopamine-treated **tumors** regressed rapidly. Histological and immunohistochemical analyses showed

inhibition of the proliferation and highly efficient induction of the **differentiation** and **apoptosis** of **tumor** cells by a non-genotoxic mechanism. No adverse effects were noted and normal skin tissue and putative stem cells that were exposed to cyclopamine together with **tumors** were well preserved under the conditions we describe. Our findings show selective and highly efficient induction of the **differentiation** and **apoptosis** of **tumor** cells in vivo by transient inhibition of the **hedgehog**/ smoothened signaling and provide a rational **cancer** therapy.
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2004295849. PubMed ID: 15196999. Induction of the **differentiation** and **apoptosis** of **tumor** cells in vivo with efficiency and selectivity. Tabs Sinan; Avci Oktay. (Yasemin Sokak Number 6, Narlidere, Izmin 35320, Turkey.. sinantas1@yahoo.com) . European journal of dermatology : EJD, (2004 Mar-Apr) 14 (2) 96-102. Journal code: 9206420. ISSN: 1167-1122. Pub. country: France. Language: English.

TI Induction of the **differentiation** and **apoptosis** of **tumor** cells in vivo with efficiency and selectivity.

AB **Hedgehog**/smoothened signaling is active in a variety of **tumors** and is also involved in the maintenance of normal stem cells in vivo. We evaluated the possibility of preferential affection of **tumor** versus normal cells following inhibition of this signaling. We applied a **cream** preparation of cyclopamine (an inhibitor of the **hedgehog**/smoothened signaling) onto skin **tumors** in patients who were scheduled for the excision of these **tumors** (four basal cell **carcinomas** and a trichoepithelioma in four unrelated patients). All of the cyclopamine-treated **tumors** regressed rapidly. Histological and immunohistochemical analyses showed inhibition of the proliferation and highly efficient induction of the **differentiation** and **apoptosis** of **tumor** cells by a non-genotoxic mechanism. No adverse effects were noted and normal skin tissue and putative stem cells that were exposed to cyclopamine together with **tumors** were well preserved under the conditions we describe. Our findings show selective and highly efficient induction of the **differentiation** and **apoptosis** of **tumor** cells in vivo by transient inhibition of the **hedgehog**/ smoothened signaling and provide a rational **cancer** therapy.
Copyright John Libbey Eurotext 2003.

CT Check Tags: Male
Aged
Aged, 80 and over
***Apoptosis: DE, drug effects**
Cell Division: DE, drug effects
***Cell Transformation, Neoplastic: DE, drug effects**
Humans
Middle Aged
Receptors, G-Protein-Coupled: AI, antagonists & inhibitors
Receptors, G-Protein-Coupled: PH, physiology
Research Support, Non-U.S. Gov't
Signal Transduction: DE, drug effects
***Skin Neoplasms: PA, pathology**
**Skin Neoplasms: PP, physiopathology**
Trans-Activators: AI, antagonists & inhibitors
Trans-Activators: PH, physiology
*Veratrum Alkaloids: PD, pharmacology

RN **4449-51-8 (cyclopamine)**

CN 0 (Receptors, G-Protein-Coupled); 0 (SMO protein, human); 0 (Trans-Activators); 0 (Veratrum Alkaloids); 0 (**hedgehog** protein, vertebrate)

L4 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

AB The invention discloses the use of cyclopamine in vivo on basal cell **carcinomas** (BCCs) to achieve therapeutic effect by causing **differentiation** of the **tumor** cells and, at the same time, **apoptotic** death and removal of these **tumor** cells while preserving the normal tissue cells, including the undifferentiated cells of the normal epidermal basal layer and hair follicles. Causation of **apoptosis** by cyclopamine is by a non-genotoxic mechanism and thus unlike the radiation therapy and most of the currently used **cancer** chemotherapeutics which act by causing DNA damage. These effects, previously unachieved by a **cancer** chemotherapeutic agent, make the use of cyclopamine highly desirable in **cancer** therapy, in the treatment of BCCs and other **tumors** that use the **hedgehog**/smoothened signal transduction pathway for proliferation and prevention of **apoptosis**.

2004:312337 Document Number 140:281377 Use of cyclopamine in the treatment of basal cell **carcinoma** and other **tumors**. Tas, Sinan; Avci, Oktay (Turk.). U.S. Pat. Appl. Publ. US 2004072914 A1 20040415, 10 pp., Cont.-in-part of WO 2002 78,704. (English). CODEN: USXXCO. APPLICATION: US 2003-682584 20031009. PRIORITY: WO 2001-TR27 20010702; WO 2002-TR17 20020419.

TI Use of cyclopamine in the treatment of basal cell **carcinoma** and other **tumors**

AB The invention discloses the use of cyclopamine in vivo on basal cell **carcinomas** (BCCs) to achieve therapeutic effect by causing **differentiation** of the **tumor** cells and, at the same time, **apoptotic** death and removal of these **tumor** cells while preserving the normal tissue cells, including the undifferentiated cells of the normal epidermal basal layer and hair follicles. Causation of **apoptosis** by cyclopamine is by a non-genotoxic mechanism and thus unlike the radiation therapy and most of the currently used **cancer** chemotherapeutics which act by causing DNA damage. These effects, previously unachieved by a **cancer** chemotherapeutic agent, make the use of cyclopamine highly desirable in **cancer** therapy, in the treatment of BCCs and other **tumors** that use the **hedgehog**/smoothened signal transduction pathway for proliferation and prevention of **apoptosis**.

ST cyclopamine **cancer** treatment; bas cell **carcinoma** treatment cyclopamine

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Smo (Smoothened), **hedgehog**/smoothened signaling; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Skin, **neoplasm**
(basal cell **carcinoma**; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT **Carcinoma**
(basal cell; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(controlled-release; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Antitumor agents
**Apoptosis**
Cell **differentiation**
Cell proliferation
**Cosmetics**

Drug delivery systems
**Neoplasm**
(cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(**gels**; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT **Hedgehog** protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**hedgehog**/smoothened signaling; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Signal transduction, biological
(**hedgehog**/smoothened; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(hydrogels; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Cell **differentiation**
(inducers; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(injections, intratumoral; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(liposomes; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Skin, disease
(nevus; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(**ointments**, **creams**; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(**ointments**; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Skin, disease
(pigmentation; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(solns., aqueous; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(systemic; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(tapes; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT Drug delivery systems
(**topical**; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT **Carcinoma**
(trichoepithelioma; cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

IT **4449-51-8**, Cyclopamine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclopamine for treatment of basal cell **carcinoma** and other **tumors**)

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L4   ANSWER 5 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
AB   The invention discloses the use of cyclopamine, a naturally occurring
     steroidal alkaloid known for over thirty years, for the treatment of
     psoriasis and achievement of rapid clearance of the psoriatic skin lesions
     together with the reversion of the histopathol. signs of disease to
     normalcy with no detectable side effects.  The cyclopamine-induced
     clearance of psoriatic lesions from the skin of patients is associated with
     the causation of cellular differentiation in lesional epidermis
     and with the rapid disappearance of CD4+ lymphocytes and other
     inflammatory cells from lesional skin.  Therapeutic compns. comprising of
     cyclopamine and a corticosteroid and/or the pre-treatment of lesions with
     a corticosteroid provide significantly further increased therapeutic
     effectiveness over the use of cyclopamine alone or a corticosteroid alone.
2004:312336   Document Number 140:315109  Use of cyclopamine in the treatment of
     psoriasis.  Tas, Sinan; Avci, Oktay (Turk.).  U.S. Pat. Appl. Publ. US
     2004072913 A1 20040415, 19 pp., Cont.-in-part of WO 2002 78,704.
     (English).  CODEN: USXXCO.  APPLICATION: US 2003-682662 20031009.
     PRIORITY: WO 2001-TR27 20010702; WO 2002-TR17 20020419.
AB   .  .  .  side effects.  The cyclopamine-induced clearance of psoriatic
     lesions from the skin of patients is associated with the causation of
     cellular differentiation in lesional epidermis and with the
     rapid disappearance of CD4+ lymphocytes and other inflammatory cells from
     lesional skin.  Therapeutic compns..  .  .
IT   CD4-positive T cell
     Cell differentiation
     Drug delivery systems
     Erythema
     Human
     Psoriasis
     Skin, disease
        (cyclopamine for treatment of psoriasis, and use with corticosteroids)
IT   Drug delivery systems
        (gels; cyclopamine for treatment of psoriasis, and use with
        corticosteroids)
IT   Cell differentiation
        (inducers; cyclopamine for treatment of psoriasis, and use with
        corticosteroids)
IT   Drug delivery systems
        (ointments, creams; cyclopamine for treatment of
        psoriasis, and use with corticosteroids)
IT   Drug delivery systems
        (ointments; cyclopamine for treatment of psoriasis, and use
        with corticosteroids)
IT   50-23-7, Hydrocortisone 4449-51-8, Cyclopamine   25122-46-7,
     Clobetasol-17-propionate   678138-50-6   678138-51-7
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (cyclopamine for treatment of psoriasis, and use with corticosteroids)

L4   ANSWER 6 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
AB   The invention relates to a process for the in vitro-directed
     differentiation of omnipotent or pluripotent cells into islet
     precursors, wherein at least one compound selected from the group consisting
     of embryonic pancreases and parts thereof, sonic hedgehog
     inhibitors, especially cyclopamin, anti-Sonic hedgehog or basic
     fibroblast growth factor, nicotinamide, LY294002, sodium tungstate,
     laminin-1 or another extracellular matrix protein and all-trans retinoic
     acid is used for the differentiation.
2003:259772   Document Number 138:234471  Process for the production of cells
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exhibiting an islet-beta-cell-like state. Escoms Bernat, Soria; Quinto Trinidad, L.; Jones, Jonathan; Haym, Anouchka Skoudy; Arribas, Francisco Real (Cardion AG, Germany). Eur. Pat. Appl. EP 1298201 A1 20030402, 19 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2001-123139 20010927.

AB The invention relates to a process for the in vitro-directed **differentiation** of omnipotent or pluripotent cells into islet precursors, wherein at least one compound selected from the group consisting of embryonic pancreases and parts thereof, sonic **hedgehog** inhibitors, especially cyclopamin, anti-Sonic **hedgehog** or basic fibroblast growth factor, nicotinamide, LY294002, sodium tungstate, laminin-1 or another extracellular matrix protein and all-trans retinoic acid is used for the **differentiation**.

IT **Carcinoma**
(embryonal; process for production of cells exhibiting an islet-beta-cell-like state)

IT **Gelatins**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for production of cells exhibiting an islet-beta-cell-like state)

IT 50-99-7, Glucose, biological studies 98-92-0, Nicotinamide 302-79-4, Retinoic acid **4449-51-8**, Cyclopamine 13472-45-2, Sodium tungstate 62031-54-3, Fibroblast growth factor 154447-36-6, LY294002
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(process for production of cells exhibiting an islet-beta-cell-like state)

L4 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

AB The invention concerns the use of cyclopamine in vivo on basal cell **carcinomas** to achieve therapeutic effect by causing **differentiation** of the **tumor** cells and, at the same time, highly efficient **apoptotic** death and removal of these **tumor** cells while preserving the normal tissue cells, including the undifferentiated cells of the normal epidermal basal layer and hair follicles. Causation of **apoptosis** by cyclopamine is by a non-genotoxic mechanism. These effects make the use of cyclopamine highly desirable in the treatment of basal cell **carcinomas** and other **tumors** that use the **hedgehog**/smoothened signal transduction pathway for proliferation and prevention of **apoptosis**
.

2002:777728 Document Number 137:257646 Use of cyclopamine in the treatment of basal cell **carcinoma** and other **tumors**. Avci, Oktay (Tas, Sinan, Turk.). PCT Int. Appl. WO 2002078703 A1 20021010, 19 pp. DESIGNATED STATES: W: AT, AU, BR, CA, CN, DE, DK, ES, FI, GB, IN, JP, MX, NO, PT, RU, SE, TR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-TR27 20010702.

TI Use of cyclopamine in the treatment of basal cell **carcinoma** and other **tumors**

AB The invention concerns the use of cyclopamine in vivo on basal cell **carcinomas** to achieve therapeutic effect by causing **differentiation** of the **tumor** cells and, at the same time, highly efficient **apoptotic** death and removal of these **tumor** cells while preserving the normal tissue cells, including the undifferentiated cells of the normal epidermal basal layer and hair follicles. Causation of **apoptosis** by cyclopamine is by a non-genotoxic mechanism. These effects make the use of cyclopamine highly desirable in the treatment of basal cell **carcinomas** and other **tumors** that use the **hedgehog**/smoothened signal

```
     transduction pathway for proliferation and prevention of apoptosis
     .
ST   antitumor basal cell carcinoma cyclopamine
IT   Antitumor agents
       Apoptosis
     Cell differentiation
     Cell proliferation
     Signal transduction, biological
        (Use of cyclopamine in the treatment of basal cell carcinoma
        and other tumors)
IT   Skin, neoplasm
        (basal cell carcinoma; Use of cyclopamine in the treatment of
        basal cell carcinoma and other tumors)
IT   Carcinoma
        (basal cell; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   Proteins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (hedgehog; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   Cell differentiation
        (inducers; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   Drug delivery systems
        (injections; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   Proteins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (smoothened; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   Drug delivery systems
        (topical; Use of cyclopamine in the treatment of basal cell
        carcinoma and other tumors)
IT   4449-51-8, Cyclopamine
     RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (Use of cyclopamine in the treatment of basal cell carcinoma
        and other tumors)
IT   4449-51-8D, Cyclopamine, derivs.
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (Use of cyclopamine in the treatment of basal cell carcinoma
        and other tumors)

L4   ANSWER 8 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
AB   The present invention makes available methods and reagents for inhibiting
     aberrant growth states resulting from hedgehog gain-of-function,
     patched (ptc) loss-of-function or smoothened gain-of-function comprising
     contacting a cell with a compound, such as a polypeptide or small mol. in an
     amount sufficient to control the aberrant growth state, e.g., to agonize a
     normal ptc pathway or antagonize smoothened or hedgehog
     activity.  The present invention further makes available methods and
     reagents for ameliorating the consequences of hedgehog
     loss-of-function, ptc gain-of-function, or smoothened loss-of-function
     comprising contacting a cell with a compound, such as a polypeptide or small
     mol., in an amount sufficient for amelioration.  In certain embodiments, the
     subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP
     phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates
     activity of the hedgehog pathway.  Thus, compds. such as
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jervine, cyclopamine, and forskolin analogs are also effective in inhibition of medulloblastoma.

2000:493313 Document Number 133:99549 Regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists. Dudek, Henryk; Ji, Benxiu (Ontogeny, Inc., USA). PCT Int. Appl. WO 2000041545 A2 20000720, 114 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US873 20000113. PRIORITY: US 1999-PV115642 19990113; US 1999-PV119594 19990210; US 1999-PV142124 19990702; US 1999-417564 19991014.

TI Regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists

AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from **hedgehog** gain-of-function, patched (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compound, such as a polypeptide or small. . . an amount sufficient to control the aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or **hedgehog** activity. The present invention further makes available methods and reagents for ameliorating the consequences of **hedgehog** loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compound, such as a polypeptide or small mol.,. . . a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the **hedgehog** pathway. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in inhibition of medulloblastoma.

ST **hedgehog** smoothened patched signal transduction regulation; cAMP analog patched agonist **hedgehog** regulation; adenylate cyclase agonist patched agonist **hedgehog**; phosphodiesterase cAMP inhibitor patched **hedgehog** regulation

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gli1; regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gli2; regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gli3; regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists)

IT Skin, **neoplasm**
Skin, **neoplasm**
(basal cell **carcinoma**, inhibitors; regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists)

IT Antitumor agents
(basal cell **carcinoma**; regulation of the **hedgehog** pathway and smoothened gain-of-function by gene patched agonists)

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IT   Gene, animal
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (hedgehog; regulation of the hedgehog pathway and
        smoothened gain-of-function by gene patched agonists)
IT   Brain, neoplasm
     Brain, neoplasm
        (medulloblastoma, inhibitors; regulation of the hedgehog
        pathway and smoothened gain-of-function by gene patched agonists)
IT   Antitumor agents
        (medulloblastoma; regulation of the hedgehog pathway and
        smoothened gain-of-function by gene patched agonists)
IT   Gene, animal
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (patched; regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
IT   Bone formation
     Cartilage
     Cell proliferation
       Cosmetics
     Drugs
     Hair
     Hematopoiesis
     Liver
     Nervous system
     Signal transduction, biological
     Skin
     Spermatogenesis
     Viscera
        (regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
IT   Muscle
        (smooth; regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
IT   Gene, animal
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (smoothened; regulation of the hedgehog pathway and
        smoothened gain-of-function by gene patched agonists)
IT   9012-42-4, Adenylate cyclase
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (activators; regulation of the hedgehog pathway and
        smoothened gain-of-function by gene patched agonists)
IT   60-92-4D, CAMP, analogs
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (agonists; regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
IT   9036-21-9, CAMP phosphodiesterase
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (inhibitors; regulation of the hedgehog pathway and
        smoothened gain-of-function by gene patched agonists)
IT   57-88-5, Cholesterol, biological studies   77-59-8, Tomatidine   78-41-1,
     Triparanol   366-93-8, AY9944   469-59-0, Jervine 4449-51-8,
     Cyclopamine   66575-29-9, Forskolin   78415-72-2, Milrinone   110452-75-0
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
     (Uses)
        (regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
IT   60-92-4D, CAMP, analogs
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (regulation of the hedgehog pathway and smoothened
        gain-of-function by gene patched agonists)
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=> s e3
L1           1 CYCLOPAMINE/CN

=> d l1 1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   4449-51-8  REGISTRY
CN   Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol,
     1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-
     3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Cyclopamine (8CI)
CN   Jervine, 11-deoxo- (7CI)
CN   Veratraman-3-ol, 17,23-epoxy-, (3β,23β)-
OTHER NAMES:
CN   11-Deoxojervine
CN   11-Deoxyjervine
FS   STEREOSEARCH
DR   11051-96-0, 26108-61-2
MF   C27 H41 N O2
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA,
       CANCERLIT, CAOLD, CAPLUS, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE,
       HSDB*, IPA, MEDLINE, NAPRALERT, NIOSHTIC, RTECS*, TOXCENTER, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); OCCU (Occurrence); PREP
       (Preparation); RACT (Reactant or reagent); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP
       (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in
       record)

Absolute stereochemistry.
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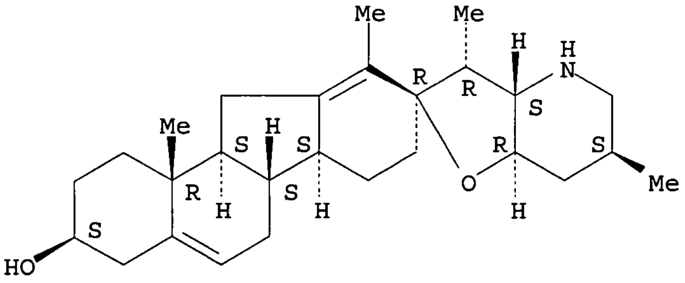

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              84 REFERENCES IN FILE CA (1907 TO DATE)
               2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              85 REFERENCES IN FILE CAPLUS (1907 TO DATE)
               2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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